

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1 (original). A compound of formula I,



wherein

R^1 represents $-R^3$ or $-A^1C(O)N(R^4)R^5$ or $-A^1C(O)OR^4$;

A^1 represents C_{1-5} alkylene;

R^2 (which replaces one of the hydrogen atoms in the amidino unit of Pab-H) represents OH, $OC(O)R^6$, $C(O)OR^7$ or $C(O)OCH(R^8)OC(O)R^9$;

R^3 represents H, C_{1-10} alkyl, or C_{1-3} alkylphenyl (which latter group is optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy, nitro or halogen);

R^4 and R^5 independently represent H, C_{1-6} alkyl, phenyl, 2-naphthyl or, when R^1 represents $-A^1C(O)N(R^4)R^5$, together with the nitrogen atom to which they are attached represent pyrrolidinyl or piperidinyl;

R^6 represents C_{1-17} alkyl, phenyl or 2-naphthyl (all of which are optionally substituted by C_{1-6} alkyl or halogen);

R^7 represents 2-naphthyl, phenyl, C_{1-3} alkylphenyl (which latter three groups are optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy, nitro or halogen), or C_{1-12} alkyl (which latter group is optionally substituted by C_{1-6} alkoxy, C_{1-6} acyloxy or halogen);

R^8 represents H or C_{1-4} alkyl; and

R^9 represents 2-naphthyl, phenyl, C_{1-6} alkoxy or C_{1-8} alkyl (which latter group is optionally substituted by halogen, C_{1-6} alkoxy or C_{1-6} acyloxy); provided that when R^1

represents R^3 , R^3 represents benzyl, methyl, ethyl, *n*-butyl or *n*-hexyl and R^2 represents $C(O)OR^7$, then R^7 does not represent benzyl;

or a pharmaceutically-acceptable salt thereof.

2 (original). A compound of formula I, as defined in Claim 1, wherein A^1 represents C_{1-3} alkylene when R^1 represents $-A^1C(O)N(R^4)R^5$.

3 (currently amended). A compound of formula I, as defined in Claim 1 or ~~Claim 2~~, wherein R^4 represents H or C_{1-6} alkyl when R^1 represents $-A^1C(O)N(R^4)R^5$.

4 (currently amended). A compound of formula I, as defined in ~~any one of Claims 1 to 3~~ Claim 1, wherein R^5 represents C_{1-6} alkyl or C_{4-6} cycloalkyl when R^1 represents $-A^1C(O)N(R^4)R^5$.

5 (currently amended). A compound of formula I, as defined in ~~any one of Claims 1 to 3~~ Claim 1, wherein R^4 and R^5 together represent pyrrolidinyl when R^1 represents $-A^1C(O)N(R^4)R^5$.

6 (currently amended). A compound of formula I, as defined in ~~any one of Claims 2 to 5~~ Claim 2, wherein A^1 represents C_{1-3} alkylene, and R^4 represents H or C_{1-3} alkyl and R^5 represents C_{2-6} alkyl or C_{5-6} cycloalkyl, or R^4 and R^5 together represent pyrrolidinyl.

7 (original). A compound of formula I, as defined in Claim 1, wherein A¹ represents C₁₋₅ alkylene when R¹ represents -A¹C(O)OR⁴.

8 (currently amended). A compound of formula I, as defined in Claim 1 or Claim 7, wherein R⁴ represents C₁₋₆ alkyl when R¹ represents -A¹C(O)OR⁴.

9 (currently amended). A compound of formula I, as defined in Claim 7 or Claim 8, wherein A¹ represents C₁₋₅ alkylene and R⁴ represents C₁₋₄ alkyl.

10 (original). A compound of formula I, as defined in Claim 1, wherein R³ represents H, C₁₋₁₀ alkyl (which latter group may be linear or, when there are a sufficient number of carbon atoms, may be branched and/or be partially cyclic or cyclic), or C₁₋₃ alkylphenyl (which latter groups is optionally substituted, may be linear or, when there are a sufficient number of carbon atoms, be branched), when R¹ represents R³.

11 (currently amended). A compound as claimed in Claim 1 or Claim 10, wherein R¹ represents H, linear C₁₋₁₀ alkyl, branched C₃₋₁₀ alkyl, partially cyclic C₄₋₁₀ alkyl, C₄₋₁₀ cycloalkyl, optionally substituted linear C₁₋₃ alkylphenyl, optionally substituted branched C₃ alkylphenyl.

12 (original). A compound as claimed in Claim 11, wherein R¹ represents linear C₁₋₆ alkyl, C₆₋₁₀ cycloalkyl, or optionally substituted linear C₁₋₃ alkylphenyl.

13 (currently amended). A compound of formula I, as defined in ~~any one of Claims 1 to 12~~Claim 1, wherein R^2 represents OH.

14 (currently amended). A compound of formula I, as defined in ~~any one of Claims 1 to 12~~Claim 1, wherein R^6 represents optionally substituted phenyl or C_{1-17} alkyl (which latter group may be linear or, when there are a sufficient number of carbon atoms, may be branched, be cyclic or partially cyclic, and/or be saturated or unsaturated) when R^2 represents $OC(O)R^6$.

15 (original). A compound as claimed in Claim 14 wherein R^6 represents optionally substituted phenyl, linear C_{1-4} alkyl, branched C_{1-3} alkyl or *cis*-oleyl.

16 (original). A compound as claimed in Claim 15 wherein R^6 represents linear C_{1-3} alkyl or branched C_3 alkyl.

17 (currently amended). A compound of formula I, as defined in ~~any one of Claims 1 to 12~~Claim 1, wherein R^7 represents optionally substituted phenyl, C_{1-12} alkyl (which latter group is optionally substituted, may be linear or, when there are a sufficient number of carbon atoms, may be branched, cyclic or partially cyclic, and/or saturated or unsaturated), or C_{1-3} alkylphenyl (which latter group is optionally substituted, may be linear or, when there are a sufficient number of carbon atoms, may be branched) when R^2 represents $C(O)OR^7$.

18 (original). A compound as claimed in Claim 17 wherein R^7 represents optionally substituted and/or optionally unsaturated linear C_{1-4} alkyl or optionally substituted and/or optionally unsaturated branched C_{3-4} alkyl, optionally substituted phenyl, or optionally substituted linear C_{1-3} alkylphenyl or optionally substituted branched C_3 alkylphenyl.

19 (original). A compound as claimed in Claim 18 wherein R^7 represents optionally substituted linear C_{1-4} alkyl or optionally substituted branched C_{3-4} alkyl, optionally substituted linear C_{1-3} alkylphenyl or branched C_3 alkylphenyl.

20 (currently amended). A compound of formula I, as defined in ~~any one of Claims 1 to 12~~ Claim 1, wherein R^8 represents H or methyl, when R^2 represents $C(O)OCH(R^8)OC(O)R^9$.

21 (currently amended). A compound of formula I, as defined in ~~any one of Claims 1 to 12 or Claim 20~~ Claim 1, wherein R^9 represents phenyl, or C_{1-8} alkyl (which latter group is optionally substituted, may be linear or, when there are a sufficient number of carbon atoms, may be branched and/or cyclic or partially cyclic) when R^2 represents $C(O)OCH(R^8)OC(O)R^9$.

22 (currently amended). A compound of formula I, as defined in Claim 20 or ~~Claim 21~~ wherein R^8 represents H or methyl and R^9 represents phenyl, C_{5-7} cycloalkyl, linear C_{1-6} alkyl, branched C_{3-6} alkyl or partially cyclic C_{7-8} alkyl.

23 (original). A compound as claimed in Claim 22 wherein R^8 represents H and R^9 represents C_{5-7} cycloalkyl, linear C_{1-6} alkyl or partially cyclic C_{7-8} alkyl.

24 (currently amended). A compound as claimed in ~~any one of the preceding claims~~ Claim 1 wherein, when R^1 represents R^3 and R^3 represents optionally substituted C_{1-3} alkylphenyl, the optional substituent C_{1-6} alkyl.

25 (original). A compound as claimed in Claim 24 wherein the substituent is methyl.

26 (currently amended). A compound as claimed in ~~any one of the preceding claims~~ Claim 1 wherein, when R^2 represents $C(O)OR^7$ and R^7 represents optionally substituted C_{1-12} alkyl, the optional substituent is selected from halogen and C_{1-6} alkoxy.

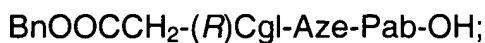
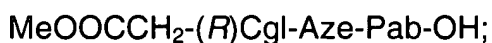
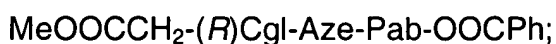
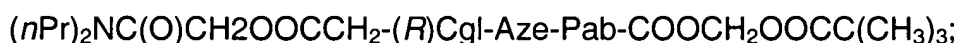
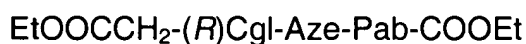
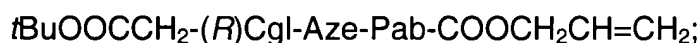
27 (original). A compound as claimed in Claim 26 wherein the substituent is selected from chloro and methoxy.

28 (currently amended). A compound as claimed in ~~any one of the preceding claims~~ Claim 1 wherein, when R^2 represents $C(O)OR^7$ and R^7 represents optionally substituted phenyl, the optional substituent is selected from C_{1-6} alkyl, C_{1-6} alkoxy and halogen.

29 (original). A compound as claimed in Claim 28 wherein the substituent is selected from methyl, methoxy and chloro.

30 (currently amended). A compound as claimed in ~~any one of the preceding claims~~ Claim 1 wherein when R^2 represents $C(O)OR^7$ and R^7 represents optionally substituted C_{1-3} alkylphenyl, the optional substituent is nitro.

31 (original). A compound as claimed in Claim 1 which is



$n\text{PrOOCCH}_2-(R)\text{Cgl-Aze-Pab-OH}$;
 $i\text{PrOOCCH}_2-(R)\text{Cgl-Aze-Pab-OH}$;
 $t\text{BuOOCCH}_2-(R)\text{Cgl-Aze-Pab-OH}$;
 $(n\text{Pr})_2\text{NCOCH}_2\text{OOCCH}_2-(R)\text{Cgl-Aze-Pab-OH}$;
 $\text{ChNHCOCH}_2\text{OOCCH}_2-(R)\text{Cgl-Aze-Pab-OH}$;
 $\text{EtOOCCH}_2-(R)\text{Cgl-Aze-Pab-OAc}$;
 $\text{HOOCCH}_2-(R)\text{Cgl-Aze-Pab-OH}$;
 $\text{HOOCCH}_2-(R)\text{Cgl-Aze-Pab-O-}i\text{-cis-Oleyl}$;
 $\text{Cyclooctyl-OOCCH}_2-(R)\text{Cgl-Aze-Pab-Z}$;
 $t\text{BuCH}_2\text{OOCCH}_2-(R)\text{Cgl-Aze-Pab-Z}$;
 $(2\text{-Me})\text{BnOOCCH}_2-(R)\text{Cgl-Aze-Pab-Z}$;
 $\text{ChCH}_2\text{OOCCH}_2-(R)\text{Cgl-Aze-Pab-Z}$;
 $\text{ChOOCCH}_2-(R)\text{Cgl-Aze-Pab-Z}$;
 $\text{PhC}(\text{Me})_2\text{OOCCH}_2-(R)\text{Cgl-Aze-Pab-Z}$;
 $(\text{Me})_2\text{CHC}(\text{Me})_2\text{OOCCH}_2-(R)\text{Cgl-Aze-Pab-Z}$;
 $\text{BnOOCCH}_2-(R)\text{Cgl-Aze-Pab-COOPh}(4\text{-OMe})$;
 $\text{ChCH}_2\text{OOCCH}_2-(R)\text{Cgl-Aze-Pab-COOPh}(4\text{-OMe})$;
 $(2\text{-Me})\text{BnOOCCH}_2-(R)\text{Cgl-Aze-Pab-COOPh}(4\text{-OMe})$;
 $\text{EtOOCCH}_2-(R)\text{Cgl-Aze-Pab-COOPh}(4\text{-Me})$;
 $\text{BnOOCCH}_2-(R)\text{Cgl-Aze-Pab-COOPh}(4\text{-Me})$;
 $\text{BnOOCCH}_2-(R)\text{Cgl-Aze-Pab-COO-}n\text{Bu}$;
 $i\text{PrOOCCH}_2-(R)\text{Cgl-Aze-Pab-COOCH}_2\text{CH=CH}_2$;
 $\text{EtOOCCH}_2-(R)\text{Cgl-Aze-Pab-COO-}t\text{Bu}$;

BnOOCCH₂-(*R*)Cgl-Aze-Pab-COO-*n*Pr;
EtOOCCH₂-(*R*)Cgl-Aze-Pab-COOCH₂OOCCh;
EtOOCCH₂-(*R*)Cgl-Aze-Pab-COOCH₂OOCCH₂Ch;
EtOOCCH₂-(*R*)Cgl-Aze-Pab-COOCH(Me)OOCPh;
EtOOCCH₂-(*R*)Cgl-Aze-Pab-COOCH₂OOCPh;
BnOOCCH₂-(*R*)Cgl-Aze-Pab-COOCH(Me)OAc;
EtOOCCH₂-(*R*)Cgl-Aze-Pab-COOCH₂OAc;
*t*BuOOCCH₂-(*R*)Cgl-Aze-Pab-COOCH₂OAc;
MeOOC-C(=CH*Et*)CH₂-OOCCH₂-(*R*)Cgl-Aze-Pab-Z;
Men-OOCCH₂-(*R*)Cgl-Aze-Pab-COOPh(4-OMe); and
EtOOCCH₂-(*R*)Cgl-Aze-Pab-COOCH₂CCl₃.

32 (original). A compound as claimed in Claim 1 which is

EtOOCCH₂-(*R*)Cgl-Aze-Pab-COOCH₂CCl₃;
BnOOCCH₂-(*R*)Cgl-Aze-Pab-COO*n*Bu;
*n*PrOOCCH₂-(*R*)Cgl-Aze-Pab-Z;
Cyclooctyl-OOCCH₂-(*R*)Cgl-Aze-Pab-Z;
EtOOCCH₂-(*R*)Cgl-Aze-Pab-COOCH₂OOCCh;
MeOOCCH₂-(*R*)Cgl-Aze-Pab-OH;
EtOOCCH₂-(*R*)Cgl-Aze-Pab-OH;
*n*PrOOCCH₂-(*R*)Cgl-Aze-Pab-OH;
*i*PrOOCCH₂-(*R*)Cgl-Aze-Pab-OH
BnOOCCH₂-(*R*)Cgl-Aze-Pab-OH; and



33 (original). A compound of formula I, as defined in Claim 1, with the additional proviso that R^1 does not represent $-A^1C(O)OR^4$.

34 (original). A compound of formula I, as defined in Claim 1, with the additional proviso that R^4 and R^5 do not independently represent H.

35 (original). A compound of formula I, as defined in Claim 1, with the additional proviso R^6 does not represent C_{1-17} alkyl, when R^2 represents $OC(O)R^6$.

36 (original). A compound of formula I, as defined in Claim 1, wherein R^1 represents $-A^1C(O)OR^4$.

37 (original). A compound of formula 1, as defined in Claim 1, wherein R^4 and R^5 independently represent H.

38 (original). A compound of formula I, as defined in Claim 1, wherein R^6 represents C_{1-17} alkyl, when R^2 represents $OC(O)R^6$.

39 (currently amended). A pharmaceutical formulation including a compound of formula I as defined in ~~any one of Claims 1 to 38~~ Claim 1, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant,

diluent or carrier.

40 (currently amended). A compound of formula I, as defined in ~~any one of Claims 1 to 38~~Claim 1, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

41 (currently amended). A compound of formula I as defined in ~~any one of Claims 1 to 38~~Claim 1, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition where inhibition of thrombin is required.

42 (currently amended). A compound of formula I as defined in ~~any one of Claims 1 to 38~~Claim 1, or a pharmaceutically acceptable salt thereof, for use in the treatment of thrombosis.

43 (currently amended). A compound of formula I as defined in ~~any one of Claims 1 to 38~~Claim 1, or a pharmaceutically acceptable salt thereof, for use as an anticoagulant.

44 (currently amended). The use of a compound of formula I as defined in ~~any one of Claims 1 to 38~~Claim 1, or a pharmaceutically acceptable salt thereof as active ingredient in the manufacture of a medicament for the treatment of a condition where inhibition of thrombin is required.

45 (original). The use as claimed in Claim 44, wherein the condition is thrombosis.

46 (currently amended). The use of a compound of formula I as defined in ~~any one of Claims 1 to 38~~Claim 1, or a pharmaceutically acceptable salt thereof, as active ingredient in the manufacture of an anticoagulant.

47 (currently amended). A method of treatment of a condition where inhibition of thrombin is required which method comprises administration of a therapeutically effective amount of a compound of formula I as defined in ~~any one of Claims 1 to 38~~Claim 1, or a pharmaceutically acceptable salt thereof, to a person suffering from, or susceptible to, such a condition.

48 (original). A method as claimed in Claim 47, wherein the condition is thrombosis.

49 (original). A method as claimed in claim 47, wherein the condition is hypercoagulability in blood and tissues.

50 (original). The use of a compound of formula I, as defined in Claim 1 but without the provisos, as a prodrug.

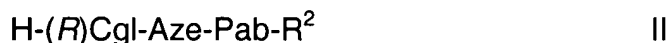
51 (original). A process for the preparation of compounds of formula I which

comprises:

(a) for compounds of formula I in which R^2 represents OH, reaction of a corresponding compound of formula I, wherein R^2 represents $OC(O)R^6$ and R^6 is as defined in Claim 1 with an alkoxide base;

(b) for compounds of formula I in which R^2 represents OH, reaction of a corresponding compound of formula I wherein R^2 represents $C(O)OR^7$ and R^7 is as defined in Claim 1 with hydroxylamine, or an acid addition salt thereof;

(c) reaction of a corresponding compound of formula II,



wherein R^2 is as defined in Claim 1 with a compound of formula III,



wherein L^1 represents a leaving group and R^1 is as defined in Claim 1;

(d) for compounds of formula I in which R^1 represents H and R^2 represents OH or $C(O)OR^7$, reaction of a corresponding compound of formula I wherein R^1 represents C_{1-10} alkyl or C_{1-3} allylphenyl, and R^2 represents OH or $C(O)OR^7$, with a base;

(e) for compounds of formula I wherein R^2 represents $OC(O)R^6$ and R^6 is as defined in Claim 1, reaction of a corresponding compound of formula I wherein R^2 represents OH, with a compound of formula IV,



or a compound of formula V.



wherein Hal represents Cl or Br and, in both cases, R^6 is as defined in Claim 1;

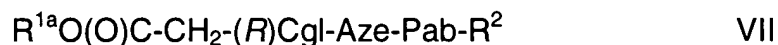
(f) for compounds of formula I in which R^1 represents H and R^2 represents

OC(O)R⁶, and R⁶ is as defined in Claim 1, reaction of a corresponding compound of formula VI,



wherein P¹ represents an acid labile ester protecting group and R² represents OC(O)R⁶, wherein R⁶ is as defined in Claim 1, with an acid;

(g) for compounds of formula I in which R¹ represents R³, R³ represents C₁₋₁₀ alkyl or C₁₋₃ alkylphenyl, and R² represents OH or C(O)OR⁷, and R⁷ is as defined in Claim 1 by a trans-esterification of a corresponding compound of formula VII,



wherein R^{1a} represents a C₁₋₁₀ alkyl or C₁₋₃ alkylphenyl group other than that being formed, or an alternative labile alkyl substituent and R² is as defined in Claim 1.